REMARKS

Claims 23-30 and 32-49 are pending in the subject application. By this Amendment, applicants have canceled claim 24 without disclaimer or prejudice, and amended claim 23 by incorporating therein an element from now canceled claim 24. Applicants have also amended claims 25, 26, 28-30, 39, 41, 42, and 44-49.

Applicants note that the amendments to claim 23 are fully supported in the specification at, *inter alia*, page 10, lines 4-15 and Fig. 6D; and page 54, line 32 to page 55, line 16. Thus, applicants maintain that these amendments do not raise any issue of new matter. The amendments to claims 25, 26, 28-30, 39, 41, 42, 44-47 and 49 are merely formatting changes to correct the dependencies of these claims, consistent with the cancellation of claim 24. The amendments to claim 48 are intended to more precisely define the epitope to which the anti-CCR5 antibody of the claimed method binds, and are supported in the specification at, *inter alia*, page 25, lines 19-26; page 52, lines 29-30 and 32-33; and page 57, lines 28-35. Thus, applicants maintain that no issue of new matter is raised by the amendments to claims 25, 26, 28-30, 39, 41, 42, and 44-49. Accordingly, applicants respectfully request that the Examiner enter this Amendment. Upon entry of this Amendment, claims 23, 25-30 and 32-49, as amended, will be pending and under examination.

The Invention

The claimed invention provides methods of reducing HIV-1 viral load in an HIV-1-infected subject which comprises administering to the subject solely after viral steady state is reached an effective viral load-reducing amount of an IgG antibody which binds to the CCR5 chemokine receptor, inhibits binding of $HIV\text{-}1_{JR\text{-}FL}$ gp120/sCD4 complex to CCR5 receptors on the surface of

$CD4^-CCR5^+$ cells, and inhibits fusion of HIV-1 to $CD4^+CCR5^+$ cells, thereby inhibiting repeated infection of the subject's cells and reducing the subject's HIV-1 viral load to 50% or less of the HIV-1 viral load prior to administration of any of the antibody to the subject.

Prior to the invention of applicants' methods, the prior art had disclosed methods of using antibodies which bind to the CCR5 chemokine receptor to prophylactically inhibit HIV-1 infection in a subject prior to the establishment of steady state HIV-1 levels in the subject. However, no anti-CCR5 antibodies had been used to therapeutically reduce viral load from steady state levels in a subject chronically infected with HIV-1.

Rejections under 35 U.S.C. §102(a) or §103(a)

The Examiner rejected claims 23, 24, 48, 28, 29, 30, 32 and 33 under 35 U.S.C. §102(a) as allegedly anticipated by or, in the alternative, under 35 U.S.C. §103(a) as obvious over Allaway et al., U.S. Patent No. 6,107,019 ("Allaway"). The Examiner stated that the claimed invention is drawn to a method of reducing HIV-1 load by administering an IgG antibody which binds to a CCR5 chemokine receptor and inhibits fusion of HIV-1 to $CD4^+CCR5^+$ cells. The Examiner also stated that the one of the embodiments is specifically directed to inhibiting $HIV\text{-}1_{JR\text{-}FL}$. The Examiner further stated that the inhibition is set forth as being reduced by various percentages of at least 50%.

The Examiner stated that Allaway teaches inhibiting HIV-1 in CD4+ cells by administering a non-chemokine agent capable of binding to a chemokine receptor. The Examiner noted that the CCR5 receptor is specifically taught at column 5, lines 35-39, as well as several other places throughout the specification. The Examiner also noted that the non-chemokine agent can be an

antibody as disclosed at column 2, lines 39-42 and column 5, lines 65-67, as well as several other places throughout the specification. The Examiner further noted that the embodiment of the HIV-1_{JR-FL} strain is taught throughout the patent.

The Examiner also stated that the reference does not specifically teach that the antibody is IgG, but asserted that this is the predominant type of immunoglobulin so it would be expected that the antibody of the reference is also of the IgG isotype. The Examiner further stated that if the antibody is not IgG, it would be obvious to produce an IgG antibody because IgG antibodies are easier to produce in large quantities than other isotypes. The Examiner additionally stated that the specific amount of reduction in viral load is a description of the desired result and an inherent property of inhibiting viral infection. The Examiner concluded that the claimed invention is thus obvious over Allaway.

In response, applicants respectfully traverse the above grounds of rejection. Applicants note that the rejected claims have been amended. However, applicants address the instant rejections as if they were being applied to the claims, as amended.

Regarding the rejection of independent claim 23 as anticipated by Allaway, applicants note that Allaway teaches a method for inhibiting HIV-1 infection of $CD4^+$ cells which comprises contacting $CD4^+$ cells with a non-chemokine agent capable of binding to a chemokine receptor in an amount and under conditions such that fusion of HIV-1 to the $CD4^+$ is inhibited, thereby inhibiting the HIV-1 infection. See, e.g., column 5, lines 24-29. Applicants note also that Allaway (1) does <u>not</u> address reduction of HIV-1 viral load; (2) does <u>not</u> refer to HIV-1-infected subjects after attainment of viral steady state; and (3) does <u>not</u> refer to administration of an agent solely after viral

steady state is reached. Thus, the method disclosed by Allaway comprises the administration of a non-chemokine agent, including an antibody, to an uninfected cell which is simultaneously or subsequently exposed to HIV-1, so as to prophylactically reduce the HIV-1 infection of that cell. By contrast, in the method claimed in the subject application, an antibody is administered to a chronically HIV-1-infected subject solely after a steady state level of HIV-1 virus has been attained, so as to therapeutically reduce the HIV-1 viral load of that subject by at least 50%. See the specification at, *inter alia*, page 96, line 15 to page 97, line 16. Applicants note that a subject in which a steady-state level of HIV-1 has been attained is chronically infected with HIV-1, and that the SCID mouse model of HIV-1 infection used in the claimed invention (in which treatment for reducing steady-state HIV-1 viral load was initiated 8-10 days post-infection; see the specification at page 96, lines 15-28) is a model of chronic HIV-1 infection.

Applicants maintain that a reduction in infection rate as disclosed by Allaway is not the same as the reduction in steady-state viral load as claimed in the subject application. Indeed, in their previous Amendment filed June 23, 2004, applicants argued to the Examiner's satisfaction (evidenced by the Examiner withdrawing the "obviousness" rejections of claims 23-25 and 28-45 set forth in the February 23, 2004 Office Action) that the prophylactic efficacy of an anti-HIV-1 antibody in protecting against acute HIV-1 infection does not predict or correlate with its therapeutic efficacy against a chronic HIV-1 infection, characterized by steady state viral levels. See arguments on pages 11-13 of the June 23, 2004 Amendment, based on data of Gauduin et al. (1997) Nature Medicine 3: 1389-93 ("Gauduin") and Poignard et al. (1999) Immunity 10: 431-8 ("Poignard"). There, applicants demonstrated that an anti-HIV-1 antibody that potently protects against infection with HIV-1 if administered prior to,

or shortly after, viral challenge (citing both Gauduin and Poignard) affords little or no therapeutic benefit in subjects in which the HIV-1 viral load had reached steady state levels prior to administration of the antibody (citing Poignard). Thus, in the present case, applicants maintain that the use of an anti-CCR5 antibody to reduce the infection of previously HIV-1-uninfected cells is different from, and does not predict the success of using an anti-CCR5 antibody to reduce the HIV-1 load in infected cells containing steady-state levels of HIV-1.

Applicants note that a finding of anticipation requires that a prior art reference teach each and every element of the rejected claims. Applicants assert that Allaway does not teach a method for (1) reducing HIV-1 viral load in (2) a chronically HIV-1-infected subject in which steady state levels of HIV-1 have been attained, (3) comprising administration of an agent to the subject solely after viral steady state is reached, as claimed in the present invention. That is, Allaway does not teach each and every element of the rejected claims. Accordingly, applicants respectfully submit that Allaway fails to anticipate pending claim 23, as amended.

Regarding the rejection of claim 23 as obvious over Allaway, applicants maintain that the Examiner has failed to establish a *prima facie* case of obviousness. According to M.P.E.P. §2142, the Examiner bears the initial burden of factually establishing a *prima facie* case of obviousness, and to do so, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the reference itself or in the knowledge of a skilled artisan, to modify the reference; (2) there must be a reasonable expectation of success; and (3) the prior art reference must teach or suggest all the claim limitations.

Applicants maintain that the Examiner fails to satisfy at least

the second and third prongs of these requirements for establishing a *prima facie* case of obviousness. In this regard, applicants contend that, first, Allaway's disclosure of a prophylactic method for inhibiting HIV-1 infection in a previously uninfected subject, in combination with the prior art, does not provide any expectation of success in using applicants' presently claimed therapeutic method for reducing steady-state viral loads in a chronically HIV-infected subject. Applicants' position is predicated on the teachings of Gauduin and Poignard which demonstrate that an anti-HIV-1 antibody which provides potent prophylactic protection against HIV-1 infection does not provide any significant therapeutic benefit in subjects chronically infected with steady state levels of HIV-1. Accordingly, applicants maintain that a skilled artisan, armed with the knowledge that an anti-HIV-1 antibody that completely protects against acute HIV-1 infection may be completely ineffective against chronic HIV-1 infection, could not have predicted and would have had no reasonable expectation of success, based on Allaway's teachings, that an anti-CCR5 antibody would prove efficacious in reducing HIV-1 viral load in subjects chronically infected with steady state HIV-1 levels.

Second, applicants reiterate that Allaway does not teach or suggest a method for (1) reducing HIV-1 viral load in (2) a chronically HIV-1-infected subject in which steady state levels of HIV-1 have been attained, (3) comprising administration of an agent to the subject solely after viral steady state is reached, as claimed in the subject invention. Thus, applicants maintain that Allaway does not teach or suggest all the elements of independent claim 23.

In view of the above remarks, applicants maintain that claim 23 is neither anticipated by, nor obvious over, Allaway. Applicants note that claim 24 has been canceled and that claims 28, 29, 30,

32 and 33, which depend, directly or indirectly, from claim 23, necessarily recite all the elements of claim 23. Applicants maintain therefore that dependent claims 28, 29, 30, 32 and 33 are also not anticipated by, nor obvious over, Allaway.

Applicants note that independent claim 48, as amended, is directed to an anti-HIV therapeutic method which recites the elements of (1) reducing HIV-1 viral load in (2) a chronically HIV-1-infected subject in which steady state levels of HIV-1 have been attained, (3) comprising administration of an anti-CCR5 IgG monoclonal antibody to the subject solely after viral steady state is reached, which elements are not taught by Allaway. In addition, claim 48 specifies that the anti-CCR5 antibody binds to an epitope which comprises amino acid residues in both the N-terminus (Nt) and in the second extracellular loop (ECL2) region of the CCR5 receptor. Applicants assert that Allaway, by contrast, does not define this specific epitope of CCR5 to which an anti-CCR5 antibody binds, nor does it suggest the use of an anti-CCR5 antibody with this specificity in a method for reducing HIV-1 viral load in a subject after viral steady state has been attained. Applicants therefore maintain that because Allaway neither teaches nor suggest all the elements of claim 48, nor provides any expectation of success in using the therapeutic method recited in claim 48, this claim is not anticipated by, or obvious over, Allaway.

Based on the remarks set forth above, applicants respectfully request that the Examiner reconsider and withdraw the instant rejections.

Rejections under 35 U.S.C. §102(b) or §103(a)

The Examiner also rejected claims 23, 24, 48, 28, 29, 30, 32 and 33 under 35 U.S.C. §102(b) as allegedly anticipated by or, in the

alternative, under 35 U.S.C. §103(a) as obvious over WO 97/47319 (Progenics).

In response, applicants respectfully traverse these rejections. Applicants note that the Examiner did not elaborate on his reasons for the instant rejections. However, applicants note that, similar to Allaway, WO 97/47319 teaches a method for inhibiting HIV-1 infection of $CD4^+$ cells which comprises contacting $CD4^+$ cells with a non-chemokine agent capable of binding to the chemokine receptor C-C CKR-5 (i.e., CCR5) in an amount and under conditions such that fusion of HIV-1 to the $CD4^+$ cells is inhibited, thereby inhibiting HIV-1 infection. See, e.g., page 16, lines 4-9. Also similar to Allaway, this method comprises the administration of a non-chemokine agent, including, *inter alia*, an antibody, to an uninfected cell simultaneous with or prior to challenge with HIV-1, so as to prophylactically reduce the subsequent HIV-1 infection of that cell. Most importantly, WO 97/47319, like Allaway, does not teach a therapeutic method for reducing HIV-1 viral load in a chronically HIV-1-infected subject comprising the administration of an antibody to the subject solely after steady state levels of virus is attained, as claimed in the subject invention.

In response to the instant rejections, applicants therefore reiterate the arguments proffered above in responding to the anticipation and obviousness rejections based on Allaway. Thus, applicants respectfully submit that since a finding of anticipation requires that a prior art reference teach each and every element of the claimed invention, and WO 97/47319 does not teach a reduction in steady state levels of HIV-1 viral load in a chronically HIV-1-infected subject as claimed in the subject invention, the Examiner's rejection of the instant claims as anticipated by WO 97/47319 is without merit.

Further, applicants maintain that claims 23, 28, 29, 30, 32, 33 and 48 are not obvious over WO 97/47319 because (1) WO 97/47319, in combination with the prior art, does not provide any expectation of success in using applicants' presently claimed therapeutic method for reducing steady-state viral load in a chronically HIV-infected subject; and (2) WO 97/47319 does not teach or suggest a method for reducing viral load in a chronically HIV-1-infected subject in which steady state levels of HIV-1 have been attained, as claimed in the subject invention, and therefore does not teach or suggest all the elements of the now pending claims.

In view of the above remarks, applicants respectfully request that the Examiner reconsider and withdraw the instant rejections.

Rejections under 35 U.S.C. §103(a)

Claims 23-30, 32-44, 48 and 49

The Examiner rejected claims 23-30, 32-44, 48, and 49 under 35 U.S.C. §103(a) as allegedly obvious over Allaway or WO 97/47319.

The Examiner stated that the invention is further limited to various routes of administration, dosages, etc. The Examiner also stated that these routes of administration, dosages, etc., are routine to adjust and would be within the skill of the artisan to optimize the method. The Examiner concluded that the instant specification is thus obvious over Allaway or WO 97/47319.

In response, applicants respectfully traverse this rejection. Applicants have argued hereinabove that independent claims 23 and 48 are not obvious over either Allaway or WO 97/47319. Briefly, applicants maintain this position because, first, the cited

references disclose prophylactic methods for inhibiting HIV-1 infection of previously uninfected subjects, which methods do not contain the elements of (1) reducing HIV-1 viral load in (2) chronically HIV-1-infected subjects in which steady state levels of HIV-1 have been attained, (3) comprising administration of an anti-CCR5 antibody to the subject solely after viral steady state is reached, as recited in the pending claims. Second, these references, either singly or in combination, do not provide any expectation of success in using applicants' claimed therapeutic method for reducing steady-state viral load in chronically HIV-infected subjects.

Applicants note that the instant rejections are based on claim elements, including routes of administration and dosages, which are recited in the dependent claims. Claim 24 has been canceled, and claims 25-30, 32-44 and 49 depend, directly or indirectly, from claim 23. Since these dependent claims necessarily recite all the elements of claim 23, applicants maintain that they too are not obvious over Allaway or WO 97/47319. Further, applicants maintain that no disclosure in Allaway or WO 97/47319 teaches, suggests or provides any expectation of success in using the specific dosage regimens recited in claims 34-43 of the subject application.

For the reasons set forth above, applicants maintain that claims 23, 25-30, 32-44, 48 and 49 are not obvious over Allaway or WO 97/47319. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the instant rejections.

Claims 23, 24, 48 and 45-47

The Examiner rejected claims 23, 24, 48 and 45-47 under 35 U.S.C. §103(a) as allegedly obvious over Allaway or WO 97/47319, each in view of Cruse et al., Illustrated Dictionary of Immunology (Boca

Raton, FL, CRC Press, Inc., 1995), page 143 ("Cruse").

The Examiner stated that the claimed invention is further limited to humanized or chimeric antibodies. The Examiner also stated that these types of antibodies are known and used in the art (citing Cruse). The Examiner asserted that one would be motivated to use these types of antibodies for the reasons given under "humanized antibody," i.e., that a humanized antibody greatly diminishes any immune response to the antibody molecule itself while retaining the desired functional capacity of reacting with the specific antigen. The Examiner concluded that the claimed invention is thus obvious over Allaway or Progenics, each in view of Cruse.

In response, applicants respectfully traverse this rejection. Applicants note that the instant rejections, relating to claims directed to the use of humanized or chimeric antibodies, are based on elements recited in the dependent claims. Applicants reiterate their contention that, as set forth in detail hereinabove, independent claims 23 and 48 are not obvious over either Allaway or WO 97/47319. Applicants maintain this position because, first, neither Allaway nor WO 97/47319 discloses a method for treating HIV-1-infected subjects containing the elements of reducing steady state HIV-1 levels in chronically HIV-1-infected subjects, comprising administration of an anti-CCR5 antibody to the subject solely after viral steady state is reached, as claimed in the present application. Second, these references, either singly or in combination, do not provide any expectation of success in using applicants' claimed therapeutic method for reducing steady-state viral load in chronically HIV-infected subjects. Applicants assert also that Cruse does not provide any teaching that overcomes the deficiencies of Allaway and WO 97/47319, i.e., Cruse clearly does not provide any disclosure relating to reduction of steady-state viral load in

chronically HIV-infected subjects.

Applicants note that claim 24 has been canceled, and that rejected claims 45-47 depend, directly or indirectly, from claim 23. Since these dependent claims necessarily recite all the elements of claim 23, applicants maintain that they too are not obvious over Allaway or WO 97/47319, in view of Cruse. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the instant rejections.

Conclusion

In summary, applicants contend that their therapeutic method of reducing viral load in a chronically HIV-1-infected subject, comprising administering an anti-CCR5 antibody to the subject solely after viral steady state is reached, is neither anticipated by nor obvious over methods disclosed in Allaway or in WO 97/47319 for prophylactically inhibiting HIV-1 infection in a cell comprising administering an anti-CCR5 antibody to the cell simultaneously with or prior to HIV-1 exposure. Since the cited references do not teach each and every element of the claimed invention, applicants maintain that the anticipation rejections are without merit. For this reason also, and moreover, because the cited references in combination with the prior art provide no reasonable expectation of success in modifying the disclosed prophylactic method to a therapeutic method as claimed in the subject application, applicants maintain that the Examiner has failed to set forth a *prima facie* case of obviousness. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejections set forth in the September 17, 2004 Final Office Action, and earnestly solicit allowance of claims 23, 25-30 and 32-49, as amended, pending in the subject application.